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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 08/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,645	ANKER ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,17,18,21,25-27,78,82 and 85-87* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,17,18,21,25-27,78,82 and 85-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-2, 17-18, 21, 25-27, 78, 82 and 85-87 are pending.

2. In view of the amendment filed 5/22/06, the following rejections remain.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-2, 17-18, 21, 25-27, 78, 82 and 85-87 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method of ameliorating or treating endotoxin-mediated TNF-α production in acute and chronic heart failure, the method comprising administering to the patient a therapeutically effective amount of ursodeoxycholic acid or ursodeoxycholic acid in combination with a diuretic and (2) a pharmaceutical formulation comprising ursodeoxycholic acid and a diuretic, **does not** reasonably provide enablement for (1) a method of ameliorating or treating any "endotoxin-mediated immune activation" in acute or chronic heart failure in a human patient comprising the steps of administering to the patient a therapeutically effective amount of ursodeoxycholic acid or ursodeoxycholic acid in combination with diuretics, (2) the said method wherein the heart failure is an acute or chronic congestive heart failure due to cardiomyopathy of unknown reason, any coronary artery disease, any vascular disease, any hypertrophic obstructive cardiomyopathy, any viral myocarditis or any genetic cardiomyopathy or dilated cardiomyopathy, (3) the said method wherein the ursodeoxcholic acid is able to decrease any cytokine production in the patient in response to endotoxin, (4) the method mentioned above wherein the ursodeoxcholic acid is able to inhibit any immune activation in the patients in response to endotoxin, (5) the said method wherein the ursodeoxcholic acid is able to reduce the permeability of the gut wall to bacteria and/or endotoxin, (6) the said method wherein the ursodeoxcholic acid is administered orally, intravenously or rectally, (7) a method of reducing elevated levels of LPS in human blood of patients suffering form acute or chronic heart failure by administering an effective amount of ursodeoxycholic acid effective to reduce the elevated levels of LPS in human blood of patients and (8) the method of reducing elevated levels of LPS in human blood of patients suffering form acute or chronic heart failure by administering an

effective amount of ursodeoxycholic acid effective to reduce the elevated levels of LPS in human blood of patients wherein the ursodeoxcholic acid is administered orally, intravenously or rectally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a method of ameliorating or treating endotoxin-mediated immune activation in acute or chronic heart failure, the method comprising the steps of measuring the level of TNF-α, endotoxin, and soluble CD14 from blood sample taken from the patient, and administering to the patient ursodeoxycholic acid or a combination of ursodeoxycholic acid and diuretics when the levels of TNF-α, endotoxin or soluble CD14 is elevated. The specification further discloses a method of reducing elevated levels of LPS induced TNF-α in human by administering ursodeoxycholic acid to the human patient with cachexia due to liver cirrhosis (page 45, Example 12).

The specification does not teach how to determine and treat any heart failure in human such as any acute or chronic congestive heart failure to any cardiomyopathy of unknown reason, any coronary artery disease, any vascular disease, any hypertrophic obstructive cardiomyopathy, any viral myocarditis or any genetic cardiomyopathy or dilated cardiomyopathy by measuring the level of any cytokine, any inflammatory marker or its production by administering to the patient any bile acid such as chenodeoxycholic acid, deoxycholic acid and cholic acid. The specification does not teach which elevated cytokines other than TNF-α, endotoxin, and soluble CD14 are associated with which heart failure mentioned above. Further, there is a lack of guidance as to which elevated inflammatory marker are associated with which heart failure in humans. There is a lack of guidance as to the effective amount of all bile acid to be administered to patient with all kinds of heart failure.

Greve et al, PTO 1449, teach not all bile acids are capable of reducing LPS mediated TNF production. Greve et al teach deoxycholic acid (DCA) in the concentration used appeared to be a strong inhibitor of TNF release by human monocytes whereas chenodeoxycholic acid (CDCA) is less effective and ursodeoxycholic acid (UDCA) is not effective at any concentration (see page 456, col. 2, Results, Figure 1, page 456, Figure 2, in particular).

With regard to claims 82 and 85-87, there is no evidence of record showing that administering any bile acid such as urosodeoxycholic acid to any human patient, or any human patient with cachexia due to liver cirrhosis or patients suffering from acute or chronic heart failure would resulted in reducing the elevated levels of LPS. The specification merely discloses elevated endotoxin levels were normalized by prolonged diuretic treatment in patient with heart failure having peripheral edema, not ursodeoxycholic acid as amended (page 37, lines 27-28).

Given the unlimited number of patient population having all sort of heart failures, the unlimited number of cytokines and inflammatory markers, it is unpredictable which bile acid is capable of reducing the elevated levels of which cytokine, which bile acid is capable of reducing the elevated levels which inflammatory maker or its production, in turn, would be useful for treating any type of heart failure. The specification is silent which cytokines is elected in "genetic cardiomyopathy". If the heart failure is genetically predisposed, there is no evidence of record that the claimed method could treat such condition simply by administering any bile acid such as the ones cited in claim 1.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 5/22/06 and the declaration of Stefan D Anker under 37 C.F.R. §1.132 have been fully considered but are not found persuasive.

Applicants' position is that claim 1 has been amended to a method for ameliorating or treating endotoxin-mediated immune activation in acute or chronic heart failure in a human

patient comprising administering to the patient a therapeutically effective amount of urodeoxycholic acid or ursodeoxycholic acid in combination with a diuretic. It is not necessary to measure the level of TNF-α in blood, because it is not significantly differ between the bloods of healthy vs. diseased patients. This is clearly shown in Figure 1. Claims 82 and 85-87 have been amended in the same manner as claim 1. As further support that the claims are properly enabled, the declaration of Stefan D Anker shows another example of an embodiment of the present invention.

In response, the amended claim 1 recites a method for ameliorating or treating endotoxin-mediated immune activation in acute or chronic heart failure in a human patient comprising administering to the patient a therapeutically effective amount of urodeoxycholic acid or ursodeoxycholic acid in combination with diuretics. The term "endotoxin-mediated immune activation" encompasses any cells activation and any endotoxin mediated production of inflammatory cytokines such as TNF-α production, IL-6 production, and/or IL-1 production. The specification discloses only a method for ameliorating or treating endotoxin-mediated cachexia in acute or chronic heart failure by administering to the patient a therapeutic amount of ursodeoxycholic acid or ursodeoxycholic acid in combination with a diuretic. The specification discloses ursodeoxycholic acid (UDCA) decreases only TNF-α production in response to endotoxin. However, the specification is silent as to which "immune activation" in acute or chronic heart failure in a human is being ameliorated or inhibited by ursodeoxycholic acid or ursodeoxycholic acid in combination with a diuretic. The specification is silent as to which cytokine other than TNF-α production in response to endotoxin is decreased by ursodeoxycholic acid. Further, the data in the declaration of Stefan D Anker show that treatment with UDCA decreases absolute neutrophil, and lymphocyte count. A decrease in the absolute number of neutrophil and lymphocyte counts does not amount to endotoxin-mediated immune *activation*. With regard to claims 82 and 85-87, there is no evidence of record showing that administering any bile acid such as ursodeoxycholic acid to any human patient, or any human patient with cachexia due to liver cirrhosis or patients suffering from acute or chronic heart failure would resulted in reducing the elevated levels of LPS. The specification merely discloses elevated endotoxin levels were normalized by prolonged diuretic treatment in patient with heart failure having peripheral edema, not ursodeoxycholic acid as amended (page 37, lines 27-28).

5. The following new grounds of rejections are necessitated by the amendment filed 5/22/06.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

7. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

"A method ...comprising the steps of ...ursodeoxycholic acid **and** ursodeoxycholic acid in combination with diuretics" in claim 1 is indefinite and ambiguous. One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention. The term "and" should have been "or". Further, the plural "steps" is consistent with the singular administering step in the claim.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1, 17, 18, 25-27, and 78 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,674,855 (of record, Oct 7, 1997; PTO 892) in view of Niebauer et al (Abstract from the 71st Scientific Sessions, Oct 27, 1998; PTO 1449) and Gennaro et al (of record, in Remington: The science and practice of Pharmacy, pages 710-713, Mach publishing company, Eston, Pennsylvania 18042, 1995; PTO 892).

The '855 patent teaches a method of treating endotoxin LPS mediated immune activation such as TNF-α production (inflammatory cytokine production) by administering to a subject such as a human (see col. 9, line 44, in particular) a therapeutically effective amount of ursodeoxycholic acid (see col. 6, line 38-41, col. 7, lines 47-49, col. 8, lines 1-7, col. 8, lines 31-34, col. 9, lines 14-21, in particular). The '855 patent teaches the invention and composition are useful in treating endotoxemia (see col. 11, lines 1-2, in particular). The reference ursodeoxycholic acid can be administered alone or in combination with other phospholipid (see col. 9, lines 57-67, in particular). The reference ursodeoxycholic acid is administered intravenously (see col. 8, line 39, in particular).

The invention in claim 1 differs from the teachings of the reference only in that the patient is a human patient with acute or chronic heart failure and the patient is administered either ursodeoxycholic acid alone or in combination with a diuretic.

The invention in claim 25 differs from the teachings of the reference only in that method wherein the bile acid is administered orally.

The invention in claim 27 differs from the teachings of the reference only in that the method wherein the bile acid is administered rectally.

Niebauer et al teach abnormal elevated levels of endotoxin (endotoxemia) are found in patient with moderate to several peripheral edema during congestive phase of chronic heart failure which is due to bacterial or endotoxin translocation (see abstract, in particular). Niebauer et al teach these patients have significant plasma levels of endotoxin and TNF-α (see abstract, in particular). Niebauer et al teach intensified diuretic treatment significantly normalizes the endotoxin levels (see abstract, in particular).

Gennaro et al teach oral route is the most convenient route for access to the systemic circulation (see page 710, col. 1, last paragraph, in particular) and rectal route is used quite frequently in and important ways of administrating a drug in pediatrics and geriatrics (see page 710, paragraph bridging col. 1 and 2, in particular). The route of administration such as rectally, or orally is within the purview of one of ordinary skill in the pharmaceutical art as taught by Gennaro et al.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer to a human subject having chronic heart failure with elevated endotoxin-mediated immune activation as taught by Niebauer et al a therapeutically effective amount of ursodeoxycholic acid alone as taught by the '855 patent or in combination with a

diuretic for a method of ameliorating or treating endotoxin-mediated immune activation as taught by Niebauer et al and/or the '855 patent. The composition is administered intravenously as taught by the '855 patent or rectally or orally as taught by Gennaro et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because oral route is the most convenient route for access to the systemic circulation (see page 710, col. 1, last paragraph, in particular) while rectal route is used quite frequently in and important ways of administrating a drug in pediatrics and geriatrics as taught by Gennaro et al (see page 710, paragraph bridging col. 1 and 2, in particular). The route of administration is within the purview of one of ordinary skill in the pharmaceutical art. One having ordinary skill in the art would have been motivated to do administer ursodeoxycholic acid as a method of treating endotoxin-mediated immune activation because the '855 patent teaches ursodeoxycholic acid is useful in treating endotoxemia and inhibits inflammatory cytokine TNF-α production caused by LPS (see col. 11, lines 1-2, in particular). Niebauer et al teach abnormal elevated levels of endotoxin (endotoxemia) and TNF-α are found in patient with moderate to several peripheral edema during congestive phase of chronic heart failure which is due to bacterial or endotoxin translocation (see abstract, in particular) and diuretic treatment significantly normalizes the endotoxin levels (see abstract, in particular).

11. Claims 21, 82 and 85-87 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,674,855 (of record, Oct 7, 1997; PTO 892) in view of Niebauer et al (Abstract from the 71st Scientific Sessions, Oct 27, 1998; PTO 1449) and Gennaro et al (of record, in Remington: The science and practice of Pharmacy, pages 710-713, Mach publishing company, Eston, Pennsylvania 18042, 1995; PTO 892) as applied to claims 1, 17, 18, 25-27, and 78 mentioned above and further in view of Schwarzenberg et al (of record, Pediatr Res 35(2): 214-217, Feb 1994; PTO 892).

The combined teachings of the '855 patent, Niebauer et al and Gennaro et al have been discussed supra.

The claimed invention in claim 21 differs from the combined teachings of the references only in that the method of treating heart failure wherein the bile acid is able to reduce the permeability of the gut wall to bacteria and/or endotoxin (lipopolysaccharide, LPS).

The claimed invention in claim 82 differs from the combined teachings of the references only in that the method of reducing elevated levels of lipopolysacchride (LPS) in human blood of patients suffering from heart failure by administering an amount of ursodeoxycholic acid effective to reduce the elevated levels of LPS in human blood of patients instead of endotoxin-mediated immune activation.

Schwarzenberg et al teach LPS can cross the intestinal barrier (gut wall) and administration of ursodeoxycholic acid (UDCA) can decrease the translocation of LPS and prevent the cytokine response as measured by TNF levels (see abstract, in particular). Schwarzenberg et al teach UDCA administered prophylactically might reduce the morbidity in clinical conditions leading to gut-derived endotoxemia (see abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the diuretic in the method of treating chronic heart failure in human that have elevated level of TNFα as taught by Niebauer et al for the bile acid such as ursodeoxycholic acid (UDCA) as taught by the '855 patent or combining the diuretic as taught by Niebauer at al with the ursodeoxycholic acid (UDCA) as taught by Schwarzenberg et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because ursodeoxycholic acid (UDCA) can decrease the translocation of LPS and prevent the cytokine response as measured by TNF levels as taught by Schwarzenberg et al (see abstract, in particular). One having ordinary skill in the art would have been motivated to administer ursodeoxycholic acid as a method of treating endotoxin-mediated immune activation because the '855 patent teaches ursodeoxycholic acid is useful in treating endotoxemia and inhibits inflammatory cytokine TNF-α production (see col. 11, lines 1-2, in particular). Niebauer et al teach abnormal elevated levels of endotoxin (endotoxemia) and TNF-α are found in patient with moderate to several peripheral edema during congestive phase of chronic heart failure, which is due to bacterial or endotoxin translocation (see abstract, in particular) and diuretic treatment significantly normalizes the endotoxin levels (see abstract, in particular).

12. No claim is allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

15. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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